ANALYSIS OF RISK FACTORS FOR EXTERNAL CONGENITAL MALFORMATIONS IN NEWBORN

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CERTIFICATE

This is to certify that the dissertation entitled "**ANALYSIS OF RISK FACTORS FOR EXTERNAL CONGENITAL MALFORMATIONS IN NEWBORN "** is a bonafide original work of **Dr. T.S. EKAMBARANATH,** in partial fulfillment of the requirements for **M.D. Branch – VII (Paediatrics)** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in September 2006.

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DECLARATION

I, **Dr. T.S. EKAMBARANATH,** solemnly declare that dissertation titled, **"ANALYSIS OF RISK FACTORS FOR EXTERNAL CONGENITAL MALFORMATIONS IN NEWBORN"** is a bonafide work done by me at Govt. R.S.R.M. Hospital during January 2005 to January 2006 under the guidance and supervision of my **Prof. Dr. L. UMADEVI, M.D., D.C.H,** Director, Institute of Social Paediatrics, The dissertation is submitted to Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – VII) in Paediatrics.**

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CONTENTS

INTRODUCTION

Parents who seek help because their child has a congenital anomaly deserve a high level of competence and sensitive understanding on the part of paediatrician. They want reliable, well informed answers and an appropriate management plan. All this demands first and foremost an accurate diagnosis. Because it allows the practitioner to identify organ system that may be involved, monitor for potential complications and predict prognosis for a patient, as well as identify other family member at risk. Recognition of conditions like trisomy 18 in a newborn alerts the pediatrician to the poor outcome associated with this condition. The diagnosis of Marfan syndrome allows for timely screening for heart disease.

Also by thorough evaluation of the antenatal history, we may be able to identify the cause of the particular anomaly, whether it is any teratogenic agent or any maternal diseases medical or surgical. By identifying the cause we will be able to reduce the incidence of congenital malformation if it is due to preventable cause.

Malformation due to diseases like gestational diabetes mellitus will alert the obstetrician also the patient for early screening and for strict glycemic control for next gestation.

Also we will be able to relieve the stress to parents by proper genetic counseling and antenatal diagnosis, by which we can plan termination of an unwarranted gestation. Also mortality due to congenital malformation is on the rise. In India congenital malformation account for 8-10% of perinatal deaths and 13-16% of neonatal

deaths[27-31]. This changing trend over years warns us that with the control of nutritional and infectious diseases congenital malformation will come to fore front as it is in west now. Latest data indicate that genetic factors contribute to approximately two thirds of condition prompting admission to children hospital[41]. Early identification of the genetic nature of a given condition may then help to appropriately focus resources for providing better care to these individuals.

REVIEW OF LITERATURE

Congenital anomalies can occur in any part of the body and most arise during the first trimester of intrauterine life. Some of these anomalies are milder or have only cosmetic significance. Congenital anomalies account for a large fraction of childhood morbidity and mortality. The incidence of congenital malformation varies based on definition and duration of study. The studies done at birth showed an incidence of 20-40 per 1000 births[8-25].

It is probably impossible and certainly unnecessary to memorize the features of all congenital defects. Instead, one can gain a foothold on this mountain of information by subdividing it into more manageable chunks. There are several ways to do this, and not all of the subdivisions are mutually exclusive.

Major congenital defects can be defined rather arbitrarily as those abnormalities, that if uncorrected, or uncorrectable significantly impair normal body function or reduce normal life expectancy.

Eg. Cleft lip, cleft palate, meningomyelocele, exomphalos, etc.

Minor anomalies are those that are of primarily cosmetic significance. These abnormalities are usually isolated, and may run in families, often with an autosomal dominant inheritance pattern. Although usually of no clinical significance to the patient, they may be helpful diagnostic clues, especially when several are found in the same patient. Most babies with three or more minor anomalies have a dysmorphic syndrome[24, 32].

The term normal variant is often applied to those physical features that fall at the far end

of the spectrum of normal configuration. Other family members may have a similar appearance but often to a milder degree, and it may be difficult to decide whether a particular features is normal or not. Nevertheless these spectrum variants have diagnostic value and should be noted when they are present. Examples include a low anterior hairline, bulbous nose, broad face, and mild proportionate short stature.

Most congenital abnormalities are isolated, affecting only a single body site. This implies that the most common failure of prenatal development occurs only in a single locality while the rest of the embryo or fetus continues to develop normally.

If the clinical evaluation shows only an isolated minor anomaly or spectrum variant in a child who is, otherwise normal, the outlook for function is usually excellent, and there are seldom concerns about occult abnormalities. A parent or sibling of the affected child may show the same structural features that help to confirm the benign nature of the anomaly and allow the clinician to point out that this is a normal feature for your family. The only interventions needed are reassurance and in some cases assistance in finding cosmetic treatment or remediation.

About two-third of all major congenital defects are isolated to a single body site. A few of these are severe enough to produce early death and the rest demand prompt intervention to minimize morbidity or later disability. The cause of each of these isolated major anomalies is believed to be multifactorial inheritance defined as the interaction between multiple genes of small effect with some subtle and presently unknown external factors. Multifactorial disorders tend to run in families in a scattered distribution, without a clear-cut Mendelian pattern. The

risk for involvement for the next child born to unaffected parents is in the range of 2-5 percent[32,33].

Multiple structural abnormalities occurring in the same child carry quite varied implications, both in terms of causation and prognosis. The possible combinations of birth defects are almost limitless but as a rule, one or two major anomalies usually are associated with several minor abnormalities. The combination of birth defects often appears to be random, but sometimes a specific pattern of anomalies can be recognized.

The underlying cause of many well-known dysmorphic syndromes remains unknown. There are four major modes of pathogenesis for congenital anomalies in humans, namely deformation, disruption, dysplasia and malformation. Each type has different implication for clinical presentation, cause, and prognosis.

Deformation describes the abnormal form, shape, or position of a part of the body that was caused by mechanical forces. Examples are clubfoot, hip dislocation, and craniofacial asymmetry. They can result from intrinsic (embryonic) or extrinsic (intrauterine) mechanical forces that alter the shape or position of an organ or part that had already undergone normal differentiation. Such factors like fetal crowding from the presence of multiple fetuses and uterine malformations, as well as oligohydramnios and a face presentation during delivery can cause them.

Risk of recurrence risk is low unless the deformation was caused by maternal uterine malformation or a fibroid.

Disruption describes a " morphologic defect of an organ, part of an organ, or larger

region of the body resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process". The classic example of a disruption is entanglement of the fetus in amniotic bands. This effect is most often seen with digits and limbs, and remnants of the bands, or constriction marks, can frequently be seen at birth.

Early disruptive lesions may heal with little scrarring, whereas those occurring late in gestation may show acute tissue breakdown persisting at birth. Therapy for these lesions is limited to restoring as much function as possible, but some degree of handicap almost always remains. Many children with disruptions have the potential for normal intellectual development and physical growth. However, surgical intervention and rehabilitative efforts are well warranted. The recurrence risk for most disruptions is very low.

Dysplasia occurs when there is "an abnormal organization of cells into tissue(s) and its morphologic results". Dysplasia tends to be tissue specific rather than organ specific (e.g. skeletal dysplasia) and can be localized or generalized.

Dysplasia tends to persist or even worsen with age. Thus, the prognosis for a dysplastic disorder depends on its natural history, because no effective therapy is available for most of these conditions. Genetic counseling is valuable in helping the parents with reproductive decision. E.g. Achondroplasia, ectodermal dysplasia.

Malformation is a term reserved for the permanent change produced by an intrinsic abnormality of development in a body structure during prenatal life. The actual mechanisms producing malformation are largely unknown, but may involve various errors in embryonic cell proliferations, differentiation, migration and programmed death, as well as cell to cell

communication. Multiple tissue types may be involved and if examined histologically, they usually have a normal appearance. Malformative processes produce a wide variety of ultimate effects, together with considerable spectrum of severity. Some process result in a structure that is too small, others produce over-growth, some show disorganization of tissues, whereas still others simply change the shape of a part of the body.

The origin of malformations is heterogenous but there is evidence to suggest that genetic aberrations play a variable but significant role in most of these abnormalities. Similarly, treatment options vary widely depending on the structures involved, the severity and type of malformation.

The occurrence of malformations can fit into one of several categories Syndrome, Sequence, Association or Field effects.

A syndrome is a "collection of anomalies involving more than one developmental regions or organ system." The word itself means a "running together" or "pattern of multiple anomalies thought to be pathogenetically related."

Further, the primary malformation itself can determine additional defects through an interrelated cascade of physical and functional processes; if ensuing malformations are related to one primary defect, factor, or event, a pathogenetic sequence has occurred. A classic example is the Pierre-Robin sequence. The recurrence risk with this isolated occurrence is negligible.

A cluster of several malformations that are not developmentally related can occur in a non-random fashion called an association that may appear without characteristic dysmorphic

features. The CHARGE association (*C*oloboma, *H*eart disease, *A*tresia choanae, *R*etarded growth and development, *G*enital anomalies, and *E*ar anomalies/deafness) is an example. It should be noted that not all features need to be present and that the extent of involvement of each system is widely variable.

These associations often manifest as sporadic rather than familial occurrences. Because they are not clearly related by a common etiology or pathogenesis, they are not considered syndromes and do not technically constitute a diagnosis. Instead, they are a recognition of a statistically significant association of features.

Another helpful concept in understanding clinical patterns of multiple birth defects is that of the developmental field complex. This term refers to anomalies of several different structures, all of which lie together in the same local body regions during embryonic development. Some adverse influence evidently affects all of these structures simultaneously because of their geographic proximity. Many recognized complexes seem to be caused by vascular abnormalities were diminished blood flow or localized hemorrhage impairs development in neighboring tissues, regardless of their embryonic origin. This results in hypoplasia or total absence of the structures involved. Such damage occurring so early in embryonic life results in permanent loss of tissue, leaving little chance of surgical correction or other effective therapy. Fortunately, the recurrence risk for these abnormalities is very low. Some examples of birth defect complexes include hemifacial microsomia, posterior axis abnormalities ranging from sacral agenesis to sirenomelia.

Evaluation of dysmorphic infant incorporates the following steps[46].

1. History – prenatal, birth

2. Family History

3. A detailed dysmorphology examination.

4. A comprehensive literature search.

PRENATAL HISTORY

A complete gestational history should be generated, including results of prenatal testing such as serum triple screen test ultrasonography, chorionic villus sampling, and amniocentesis. The maternal age at conception should be documented, because the risk of chromosomal anomalies such as improper separation and nondisjunction rises with maternal age. It is important to identify prenatal exposures to infection and medications, maternal habits such as alcohol and drug use, maternal chronic illnesses, and pregnancy-related complications. It is also important to identify exposure to environmental agents that might act as teratogens.

This information is critical, because the counseling and calculation of recurrence risk for a given malformation are vastly different if environmental exposures are involved.

BIRTH HISTORY

Another important component of the gestational history is obtaining information on fetal activity, size, and position. Often, the mother's subjective impressions can be further confirmed by examining obstetric records of the perinatal period. A history of hypotonia may be further supplemented by reports of poor fetal movements and breech presentation. Perinatal

information including gestational age, fetal position at delivery, the length of labour and type of delivery, and any evidence of fetal distress, such as passage of meconium, are all relevant data. Apgar scores, the need for resuscitation, birth parameters, any malformations noted at birth, and all abnormal test results should be noted.

FAMILY HISTORY

A critical part of any genetic evaluation is to obtain the family history. Special attention should be paid to consanguinity, and any first-degree relatives with similar malformations to those of the patient being evaluated, also known as the index case, or an extended family history should be used to identify relatives with congenital anomalies, developmental abnormalities, or physical differences.

Reproductive histories, especially of the parents, should be elicited. Specifically, questions should be asked about infertility, miscarriages, and stillbirths. The occurrence of more than two first-trimester miscarriages increases the probability of finding a balanced translocation in one parent.

Obtaining a formal family history is helpful in bringing out information that is often critical to making a diagnosis. Positive responses may help discern the mendelian pattern of inheritance of given genetic disorder. For example, a disease affecting every generation, with both males and females involved, such as Marfan syndrome, would most likely be autosomal dominant. A pattern of X-linked recessive disease, such as hemophilia, would show affected males related through unaffected or minimally affected females; transmission in this pattern should not occur from father to son.

PHYSICAL EXAMINATION FOR DYSMORPHOLOGY

The assessment should begin with newborn growth parameters that can reflect the degree of any prenatal insult. Measurements such as height, weight (usually reflecting

nutrition), and head circumference should be taken.

A complete physical examination should include assessment of patient anatomy for features varying from usual or normal standards. This assessment can often provide clues to embryologic mechanisms. The data obtained should then be interpreted with respect to normal standards using comprehensive standard tables that are available for these purposes. Special attention to familial variants should be given.

The shape and size of the head and fontanels should be noted as well as the cranial sutures, with assessment for evidence of craniosynostosis or an underlying brain malformation. Any scalp defects should also be noted. The shape of the forehead, appearance of eyebrows (noting synophrys, or "mono-brow"), and the texture and distribution of hair should be noted. The spacing of the eyes, or canthal measurements, the interpupillary distances, palpebral fissure lengths, presence or absence of colobomata and epicanthal folds, and noting whether the palpebral fissures are turned upward or downward are components of the dysmorphology examination. Examination of the ears should include a search for preauricular and postauricular pits, or ear tags, and assessment of the placement, and folding of the ear is important. Each development occurs in a temporal frame similar to that of the kidneys, and often, external ear anomalies are associated.

Evaluation of the nose should cover the shape of nasal tip, the alae nasi, presence of anteverted nares, the length of the columella, and patency of the choanae. The mouth and throat are examined for the presence of a cleft lip or palate; the shape of the palate and uvula are noted, and the presence of unusual features, such as tongue deformities, lip pits, frenula, and

natal teeth, are recorded. A small retrognathic or receding chin which can be a part of several syndromes or an isolated finding, should be noted. The neck is inspected for excess nuchal folds or skin and evidence of webbing. Any bony abnormalities in the neck should prompt an evaluation of the cervical vertebrae to confirm cervical and airway stability.

The umbilicus should also be examined, with any hernias as well the number of vessels present in the newborn cord noted. A two-vessel cord, in which only a single artery is present, can be associated with renal anomalies. The genitourinary examination concentrates on determining whether anomalies such as hypospadias, chordee, cryptorchidism, microphallus, and ambiguous genitalia are present. These external anomalies may be associated with internal anomalies involving the upper urinary tract as well. The anus is examined for evidence of tags, its placement, and its patency.

The back should be assessed especially for the shape of the spine and any associated defects, such as myelomeningocele. These defects prompt further radiologic evaluation to assess for potential functional limitations. Additionally, a sacral dimple or hair tuft at the base of the spine should be noted because either could signify developmental abnormalities in the underlying neural tissue.

Minor anomalies are often manifested in the extremities. Gross differences in the hands and feet include polydactyly (more than five digits); whether the extra digits are located in a pre-axial or post-axial position should be noted, syndactyly (fusion of the digits), clinodactyly (incurving of the digits).

An examination of the skin is also important, to look for phakomatoses or skin

manifestations that herald the presence of an underlying disorder. Examples are café-au-lait spots and ash leaf spots. Hemangiomas, irregular pigmentation, and skin diseases are noteworthy.

According to Mishra P.C. and Baveja R. [15] a prospective study of 4098 births the incidence of congenital malformations was 1.464 per 100 births. Major malformations were seen in 1.1% births and minor malformations in 0.4% births. Patterns of congenital anomalies included multiple anomalies (37.68%), CNS malformations (13.33%), alimentary tract anomalies (6.66%), cardiovascular malformations (8.99%), genitourinary malformation (6.66%), limb anomalies (13.33%), and anomalies of skin and appendages (13.33%). Factors like maternal age, hormone testing and drug ingestion during pregnancy, radiation exposure and maternal infections were identified as possible risk factors for congenital malformations in the newborn.

According to Patel Z.M. et al [2] congenital malformations had become important causes of perinatal mortality with improved control of infection and nutritional deficiencies. They account for 10-15% of neonatal deaths. A national collaborative community based study of ICMR reported that congenital malformations accounted for 6.6% of neonatal deaths in the slum dwellers. [17]. An overall incidence of congenital malformations was 1.63%. This is also consistent with other reported studies from various parts of India. [4], [7], [15], [16], [17], [18].

Analysis of an overall distribution of malformations in this study showed that central nervous system was the commonest system involved. [19], [20]. Consanguinity was found in 8.1%. The incidence of polygenic malformation ranked as high as 45%. Incidence of cleft lip, cleft

palate and polydactyly compared well with the established data. 65% of malformations had genetic basis. Chromosomal disorders constituted 4%. The incidence of Trisomy 21 was 1 in 1200 at the age of 25.

Regarding maternal factors and malformations the incidence of congenital malformations was higher in mothers > 35 years of age and when babies were < 1000 gm in weight. Autosomal dominant conditions were found in 12% and recessive in 4%.

A study was conducted by Asha Bai P.V., John T.J., and Subramaniam V.R. [22] on the effect of consanguinity on fertility, reproductive loss and developmental disorders were studied in 156 consanguineous marriages in comparison with 221 non-consanguineous marriages were studied. Although fertility was greater (P less than 0.05) in consanguineous than in non-consanguineous marriages, the number of living children were approximately equal in both groups, on account of increased child mortality in the former (P less than 0.05). The frequencies of abortion and stillbirth were (also) approximately equal in both groups. Developmental anomalies were significantly more frequent (P less than 0.001) among the offspring of consanguineous parents. These results indicate the continued presence of deleterious genes in this population, in spite of the practice of consanguinity over many generations.

Martinez-Frias M.L., Bermejo E. and Frias J.L. [21] presented an analysis of deformations observed in a series of 26,810 consecutive infants with congenital defects. They observed that

3.88% of these infants had deformations, for a prevalence figure of 0.07% live-born infants. Deformations of extrinsic cause were more frequently isolated defects and had a better prognosis, while deformations of intrinsic origin were more frequently associated with other congenital anomalies and, generally, had a poor prognosis.

AIM OF THE STUDY

- To find out the incidence of congenital malformations during the 1 year period in consecutive deliveries.
- To find out the association of malformations in relation to various maternal factors such as age, parity and various antenatal risk factors.
- To find out the contribution of consanguinity in the occurrence of congenital malformations.
- To find out the association of malformation in relation to the birth weight, gestational age, sex of the baby, live and still birth.

MATERIALS AND METHODS

This is a prospective, descriptive study conducted at Raja Sir Ramasamy Mudaliar

Lying in Hospital, a maternity hospital attached to Govt. Stanley Medical College, Chennai. Twelve thousand one hundred and eight babies born during the period of Jan 2005 to Jan. 2006 were taken into study.

All the mothers were interrogated within 48 hours of delivery as per the proforma prepared. The proforma contained the particulars like maternal age, consanguinity, education, socioeconomic status, and antenatal history in detail with reference to drug intake, fever, and exposure to irradiation. Medical diseases complicating pregnancy like Diabetes, Heart disease, and hypertension were also taken into account. A detailed obstetric history with reference to previous abortions and stillbirths were taken from the mother.

Information was obtained on fetal activity, size and position. Perinatal information including gestational age, fetal position at delivery, duration of labor, type of delivery and any evidence of fetal distress was obtained.

A comprehensive family history comprising of three-generation pedigree was elicited. Any member in the family having similar or any other anomaly was considered. Reproductive history especially about infertility, miscarriages, and stillbirth were inquired.

A complete physical examination of all new born including assessment of patient's anatomy for features varying from usual or normal standards was performed. Measurements such as height, weight, and head circumference were taken in comparison with standard charts. The shape and size of the head and fontanels as well as the cranial sutures was noted, with assessment for evidence of craniosynostosis or an underlying brain malformation. Spacing of the eyes and presence or absence of coloboma was noted.

Ears were examined for presence of pre auricular tags, sinuses, pits or abnormal creases. They were also assessed for placement, length and folding. Evaluation of nose covered the shape of nasal tip, the ala nasi, presence of anteverted nares, patency of choanae. The mouth and throat were examined for the presence of cleft lip and palate; the shape of palate and uvula were noted, and the presences of unusual features like nasal teeth were recorded. Retrognathia or receding chin, which could be a part of a syndrome, was also noted. Neck was inspected for nuchal folds or webbing.

Evaluation of chest and thorax including lung auscultation and cardiac examination was done. Any obvious thoracic deformity was noted. Abdominal examination was focused on determining any defect in anterior abdominal wall like exomphalos, deficient anterior abdominal wall muscles. Any presence of organomegaly was documented. Umbilicus was also examined for hernia as well as number of vessels present in newborn cord.

Genitourinary examination was concentrated on determining whether anomalies such as hypospadiasis, cryptorchidism, microphallus and ambiguous genitalia were present. The anus was examined for evidence of tags, its placement and patency.

The back was also examined especially for the shape of the spine, any associated defects such as meningomyelocele, natal cleft, etc. Hands and feet were assessed for polydactyly, syndactyly, and clinodactyly. Examination of skin for phakomatoses like café au lait macules, hemangiomas, port-wine stains was done.

Investigations like hemoglobin estimation, blood grouping and Rh typing was done in mother. Radiographs, ultrasonogram, and echocardiogram were done in babies for selective

cases.

The anomalies were grouped and categorized as syndrome, sequence, association or field defect. They were also classified as major, minor, or normal variant. All these datas were tabulated and analyzed statistically.

OBSERVATION

A total of 12108 deliveries took place in a period of one year from Jan 2005-Dec2005 at R.S.R.M. Hospital, Chennai. The number of live-births was 11881 and the number of stillbirths was 227. The incidence of congenital malformation was 30.06 per 1000 birth (365 cases). Among them, major malformations were present in 17.92 per 1000 births (217 cases), while minor malformations 10.57 per 1000 births (136 cases).

All the results were tabulated and analysed statistically. Demographic and clinical variables in the qualitative form were expressed as frequencies with their percentages.

Association between type of anomalies with demographic / clinical variables were analysed using Pearson chi-square test, Yates corrected chi-square test and chi-square trend test as wherever appropriate and odds ratio with 95% confidence interval were given.

Table – 1

Frequency of Anomalies in Live and Still Birth

Baby	Normal babies	No Of Malformed Babies	% Of Malformed Babies
Live	11881	325	2.73
IUD/still birth	227	22	9.69*

* p value = 0.001

Congenital malformations were seen more in stillbirths as compared to live-births, the frequency being 9.69% and 2.73% respectively. 18 malformed babies died in the neonatal period.

The chi-square value for these data was 31.23 with p value being 0.001 which is statistically significant. The odds ratio computed as 3 (2-5). This shows that the occurrence of congenital anomalies is significantly higher in still births.

Table – 2

Classification of Anomalies

Type of Anomaly	No Of Malformed Babies	% Of Malformed Babies
Major	217	1.79
Minor	136	1.12
Normal variant	12	0.09

Table - 3

Sex Distribution and Congenital Malformations:

Sex	Normal babies	No Of Malformed Babies	% Of Malformed Babies	Total babies
Male	5993	214*	3.38	6207
Female	5750	146	2.54	5896

* p value = 0.001

Among the malformed babies 214 were male and 146 were female. Three babies had ambiguous genitalia. For two babies sex could not be identified . 1 case of caudal regression syndrome, the limbs were fused and genitals could not be visualized. 1 case of exomphalus major also genitals could not be identified.

The chi-square value for these data was computed to be 9.89 and p value 0.001, which was statistically significant. The odds ratio was 1.4 (1.1 – 1.8) which shows that males have 1.4 times more risk compared to females.

Table – 4
Distribution of Malformations According to the Maternal Age

Mother's age	Normal babies	No Of Malformed Babies	% Of Malformed Babies	Odds Ratio
<20	1495	36	2.35	1.00
20-30	8905	272	2.96	1.27
30-35	1106	36	3.15	1.35
>35	237	21	8.13	3.68*

* p value = 0.002

Mothers were classified according to their age into four groups. The incidence of malformed babies was found to be highest in the age group above 35 years, which is 8.13%. Statistical analysis of the data by Chi- Square trend shows that the risk of malformations increases proportionally with age, with the greatest risk suggested for the above-35 age group. The Chi-square trend value for the data was computed to be *13.45*, and the *p* value was computed to be *0.002*, which is statistically significant.

Table - 5

Consanguinity and Congenital Malformations

Consanguinity	No of Malformed Babies	% of Total malformed babies
Non consanguinity	245	67.1%
II degree	76	20.8%
III degree	44	12.1%

67.1% of babies with congenital malformations were born of non-consanguineous marriage as compared to 32.9% in the consanguineous group.

Table - 6

Distribution of cases according to parity

Parity	Normal babies	No of Malformed Babies	% of total Malformed Babies	Odds Ratio
1	5121	193	3.76	1.00
2	4122	101	2.45	0.65
3	1986	49	2.47	0.65
≥ 4	514	22	4.28	1.14*

* p value = 0.05

According to the parity, mothers were classified into four groups. It was observed that after the first child, there is an increase in incidence of congenital malformations among mothers with parity four and above. The Chi-Square trend values for this set of data were *4.01,* and the *p* value was *0.05.* Our observations suggest that there is a significant correlation between the parity and incidence of congenital malformations.

Table - 7
Distribution of cases according to mode of delivery

Mode of Delivery	Normal Babies	No of Malformed Babies	% of total Malformed Babies
Normal	9114	223	2.38%
Forceps	334	31	8.49%
LSCS	2295	111	4.61%

Out of 12108 deliveries, 223 babies were delivered through normal labour and 111 were delivered through LSCS. The incidence of malformations was found to be more in cases of forceps and LSCS deliveries.

Table - 8
Correlation of antenatal factors with congenital malformations

Types of Antenatal Risk Factors	No of Malformed Babies	% of total Malformed Babies
Nil	331	90.7%
Drugs		
NSAID	24	6.6%
For termination	10	2.7%
Fever		
No fever	337	92.3%
Fever without rash	22	6.0%
Fever with rash	6	1.6%

Out of 365 malformed babies, only 9.3% had history of drug intake during antenatal period and 7.6% of malformed cases had fever with or without rash.

Table - 9

Complications during pregnancy and congenital malformation

Medical / Surgical / Gynaec	No of Malformed Babies	% of total Malformed Babies
No Illness	327	89.6
PIH	21	5.8
Placenta Previa	7	1.9
GDM	3	.8
Fibroid	4	1.1
Placental Calcification	1	.3
Heart Disease	2	.5
Oligo / Polyhydramnios		
Nil	328	89.9
Oligohydramnios	21	5.8
Polyhydramnios	16	4.4

On evaluation of maternal medical/ gynaecological illness, 327 people had no illness during antenatal period and 38 had illness. Out of 38 mothers, 21 had PIH, 7 had placenta previa, 4 had fibroid, 3 had GDM, 2 had heart disease and one had placental calcification

Out of three malformed babies born to a gestational diabetes mother, two had CTEV and one had caudal regression syndrome.

21 mothers of malformed babies had oligohydramnios, 16 had polyhydramnios.

Table - 10

Gestational age and congenital malformation

Gestation	Normal Babies	No of Malformed Babies	% of total Malformed Babies
Term	10488	324	3.31
Pre-term	1240	41	3.31
Post-term	15	0	0

Analysis of the data obtained regarding gestational age and congenital malformations by Chi-Square trend showed that there is no statistically significant difference between the incidence of congenital malformations and the gestation age. The Chi-Square value for this set of data was *0.16*, with the *p* value computed to be *0.68*.

Table - 11

Birth Weight and Malformations

Birth Weight (Kg)	Normal Babies	No of Malformed Babies	% of total malformed babies	Odds Ratio
2.5-3.5	7980	211	2.58	1.00
<1	45	3	6.35	2.52
1-1.5	135	24	15.09	6.72*
1.5-2.5	2793	125	4.28	1.69
>3.5	790	2	0.25	0.10

* p value = 0.02

From the observed data, the incidence of congenital malformations was observed to be more when the birth weight was less than *1.5kg*. The chi-square trend value was computed as 5.09 with p value was found as 0.02 which is statistically significant. Hence weight < 1.5 kg is a significant risk factor for congenital malformations.

Table - 12
Systemic distribution of Congenital Malformations

Malformations	No	% Of MB	LB	SB	NND	N/1000 birth
Gastrointestinal system	92	25.20	76	8	8	7.59
Genitourinary system	43	11.78	39	4	0	3.55
CNS	47	12.27	27	12	8	3.88
Musculoskeletal	105	28.76	87	12	6	8.67
Skin	30	8.2	28	1	0	2.47
Miscellaneous - Minor	43	11.78	43	0	0	3.55
Miscellaneous – Major	8	2.19	6	2	0	0.6

MB : Malformed Babies
LB : Live brith
SB : Still-birth
NND : Neonatal Death

The commonest system involved was the musculoskeletal (8.67/1000 birth) followed by GIT(7.59/1000 birth), CNS (3.88/1000 birth) and genitourinary (3.55/1000 birth).

Table - 13
Gastrointestinal system Anomalies

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre Term	N/1000 Births
eft lip	14	3.83	13	0	1	12	2	10	4	1.15
eft palate	14	3.83	13	1	0	7	7	13	1	1.15
eft lip and palate	24	6.57	23	0	1	16	8	23	1	1.98
xomphalos	4	1.09	1	1	2	2	1	3	1	0.33
ngle umbilical artery	8	2.19	6	1	1	6	1	4	4	0.67
sophageal atresia	4	1.09		3	1	3	0	2	2	0.33
uodenal atresia	1	0.27	0	0	1	1	0	1	0	0.08
emangioma liver	1	0.27	1	0	0	1	0	0	1	0.08
nal atresia	9	2.46	7	1	1	7	2	7	2	0.74
ernia	3	0.82	3	0	0	2	1	3	0	0.25
estibular fistula	7	1.92	6	1	0	0	7	6	1	0.58
AOM palsy	3	0.82	3	0	0	0	3	3	0	0.25

On analyzing the anomalies in gastrointestinal system, cleft lip and palate formed the major group (24 cases). One baby died in the neonatal period. Cleft lip and palate account for 14 each. In this study, anomalies were more common in males rather than in females except for vestibular fistula and DAOM palsy. Most of the malformations were common in term babies except in single umbilical artery in which there was an equal distribution among term and preterm. One case of hemangioma liver was reported. There were 9 cases of anal atresia, of

which one died in neonatal period and other was a stillbirth. Both single umbilical artery and esophageal atresia were found in two babies, one was a stillbirth and the other died in the neonatal period.

Table - 14
Genitourinary System Analysis

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre term	N/1000 Births
Hydronephrosis	4	1.10	3	1	0	3	1	4	0	0.33
Polycystic kidney	1	0.27	1	0	0	0	1	0	1	0.08
Hypospadias	14	3.83	14	0	0	14	0	14	0	1.15
Micropenis	5	1.37	3	2	0	5	0	4	1	0.41
Undescended testis	10	2.74	9	1	0	10	0	10	0	0.82
Hydrocoele	4	1.10	4	0	0	4	0	4	0	0.33
Ambiguos genitalia	3	0.82	3	0	0	*	*	3	0	0.25
Labial adhesion	2	0.55	2	0	0	0	2	1	1	0.17

Major anomalies in genitourinary system were analysed, of which hypospadias had the highest occurrence. Undescended testis ranked second in this group. Hydronephrosis and hydrocele constitutes 4 each. In hypospadias no death were reported. In undescended testis, one stillbirth known to have prune belly syndrome was recorded. All cases of hydronephrosis, hypospadias and UDT were found to occur in term babies. Three cases of ambiguous genitalia were noted in live and term babies. Two cases of labial adhesion were found in live female babies of which one was term and other was preterm.

Table - 15
Musculoskeletal System Analysis

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre term	N/1000 Births
Polydactyly	45	12.33	41	2	2	20	24	34	11	3.71
Ctev	32	8.77	27	4	1	21	10	27	5	2.64
Valgus deformity-foot	8	2.19	7	1	0	5	3	6	2	0.67
Rocker bottom feet	5	1.36	4	0	1	2	2	5	0	0.41
Acromelia	5	1.36	5	0	0	0	5	5	0	0.41
Phocomelia	2	0.55	0	1	1	2	0	1	1	0.16
Arthrogryposis	3	0.82	0	3	0	2	1	2	1	0.25
Osteogenesis imperfecta	1	0.27	0	0	1	0	1	1	0	0.08
Achondroplasia	1	0.27	1	0	0	0	1	1	0	0.08
Amniotic band	1	0.27	1	0	0	1	0	1	0	0.08
Caudal regression syndrome	1	0.27	0	1	0	*	*	0	1	0.08
Ehler Danlos syndrome	1	0.27	1	0	0	1	0	1	0	0.08

Among the musculoskeletal system anomalies, polydactyly (preaxial, postaxial or intercalary) constitutes the major group. In this category two neonatal death and two stillbirths were reported. CTEV malformations represent the second highest among these musculoskeletal malformations.

Of 32 cases 4 were stillbirth and 1 died in neonatal period. More cases were reported to occur in males and in term babies. Valgus deformity foot was found to occur in 8 cases of which one was stillbirth and rests were alive. 5 term babies were found to have rocker bottom

feet of which one died in immediate neonatal period. Phocomelia was found in two cases, of which one was neonatal death and other was stillbirth. Osteogenesis imperfecta was seen in a term female baby.

Table - 16
Cutaneous Malformations

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre Term	N/1000 Births
Café au lait macules	13	3.56	13	0	0	7	6	12	1	1.07
Port wine stain	5	1.36	5	0	0	3	2	5	0	0.41
Hemangioma	2	0.55	2	0	0	0	2	2	0	0.16
Aplasia cutis congenita	2	0.55	2	0	0	2	0	2	0	0.16
Branchial sinus	2	0.55	1	1	0	2	0	2	0	0.16
Incontinentia pigmenti	1	0.27	1	0	0	0	1	1	0	0.08
Ectodermal dysplasia	1	0.27	1	0	0	1	0	1	0	0.08
Large black mole	4	1.10	3	0	0	2	1	3	0	0.33

Phacomatosis constitutes the major group of which café au lait macules had the highest occurrence. 13 cases of café au lait macules, 5 cases of port wine stain and 2 cases of hemangioma were noted. Two cases each of branchial sinus and aplasia cutis congenita were reported. One case was reported in each category of incontinentia pigmenti and ectodermal dysplasia.

Table - 17
Analysis of Central Nervous System Malformations

Malformations	No	%OF MB	LB	SB	NND	M	F	Term	Pre term	N/1000 Births
Meningomyelocele	21	5.75	11	5	5	18	3	20	1	1.73

Hydrocephalus	11	3.01	9	1	1	7	4	11	0	0.90
Anencephaly	8	2.19	0	6	2	5	3	6	2	0.67
Encephalocele	1	0.27	1	0	0	1	0	1	0	0.08
Natal cleft + Hypertrichosis	4	1.10	4	0	0	2	2	4	0	0.33
Craniosynostosis	1	0.27	1	0	0	1	0	1	0	0.08
Lipoma- lumbar spine	1	0.27	1	0	0	1	0	1	0	0.08

Among the CNS malformations, Meningomyelocele was found in the majority of the cases. Out of 21 cases, 5 were stillbirth and 5 neonatal deaths and the rest were live birth. Hydrocephalus constitutes 11 cases and one neonatal death and stillbirth were reported. The incidence of hydrocephalus was bit higher than anencephaly. Of 8 cases of anencephaly, 6 were stillborn and two died in the immediate neonatal period. Two were preterm and 6 were term. One case each of craniosynostosis, lipoma lumbar spine and encephalocele was also reported. Anomalies were more common in males than in females except natal cleft where there was an equal distribution.

Table - 18
Minor Malformations

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre term	N/1000 Births
Preauricular tag	18	4.9	18	0	0	7	11	16	2	1.49
Preauricular sinus	2	0.55	2	0	0	2	0	2	0	0.16
Ear pits	6	1.64	6	0	0	3	3	6	0	0.49

Clinodactyly	4	1.10	4	0	0	2	2	4	0	0.33
Large incurved toe	2	0.55	2	0	0	1	1	2	0	0.16
Vestigeal thumb	2	0.55	2	0	0	1	1	2	0	0.16
Cleft tragus	4	1.10	4	0	0	1	3	4	0	0.33
Dermoid	2	0.55	2	0	0	1	1	2	0	0.16
Coloboma-iris	1	0.27	1	0	0	1	0	0	1	0.08
Heterochromia- iris	2	0.55	2	0	0	2	0	2	0	0.16

Ear malformations represent the highest among the minor malformations. There were 5 cases with anomalies in eye like heterochromia iris, coloboma and dermoid. There were no stillbirths and neonatal death reported in babies with minor malformations. Majority of babies were term.

Table - 19
Miscellaneous - Major Anomalies

Malformations	No	% of MB	LB	SB	NND	M	F	Term	Pre term	N/1000 Births
Microtia	5	1.36	4	1	0	4	1	5	0	0.41
Microphthalmia	2	0.55	2	0	0	1	1	2	0	0.16
Cataract	1	0.27	0	1	0	1	0	0	1	0.08

In this category, microtia, microphthalmia and cataract were considered. Of them microtia constitutes 5 cases, of which one was still birth and rest were live-birth. Two cases of Microphthalmia were reported of which both were live birth. One case of cataract, which was a stillbirth, was also reported

DISCUSSION

Among 12108 births during the study period, 11881 were live births and 227 were stillbirths. The frequency of congenital malformations in the present study was 3.01% (365 cases). Incidence among live births is 2.73% (325 cases) and incidence among stillbirths is 9.69% (22 cases). The incidence of congenital malformations was significantly higher in stillbirths compared to live births

Of these 1.79% (217 babies) had major anomalies and 1.12% (136 babies) had minor anomalies.

These rates in the present study are comparable to the incidence of congenital malformations in other hospital-based studies of live and stillbirths.

In a study by Vikram Datta et. al.[1],out of the total 2968 deliveries, 2869 were live and 99 were stillbirths. The number of babies with congenital malformations diagnosed at birth or within the first week of life was 37 (1.24%), while the total number of malformations were 48. Out of these 26 (70.3%) babies had 34 major anomalies and 11 babies (29.7%) had 14 minor anomalies.

In another study conducted by Patel Z.M. et. al. [2] Out of 17,653 consecutive births, 294 (1.6%) had a major malformation and 1400 (7.92%) had minor malformation. Amongst 17,653 births, 328 (1.85%) were stillbirths, out of which 52 (15.8%) were malformed. Malformations led to early death in 40 (13.6%). The incidence of congenital anomalies was higher amongst still born than among live babies.

According to Bhat B.V et. al. [8], musculoskeletal, cutaneous and genitourinary malformations were common among live born babies while central nervous system and gastrointestinal defects were common among still born babies

SEX DISTRIBUTION:

Among the malformed babies 210 were male and 150 were female. Male: female ratio was 1.4 and it was statistically significant.

In a study conducted by Vikram Datta et. al.[1] and Verma et. al. [4], no difference was observed in the distribution of malformations between the two sexes.

CONSANGUINITY AND CONGENITAL MALFORMATIONS

67.1% of babies with congenital malformations were born of non- consanguineous marriage as compared to 32.9% in the consanguineous group.

Out of 52 cleft palate +/- cleft lip, 22 cases were reported in consanguineous marriages. 7 cases of preauricular tags were found in consanguineous marriage against 11 in non-consanguineous. Anal atresia was found in 4 cases of consanguineous marriages out of the total 9 cases. Out of 45 cases of polydactyly, 20 cases had parental consanguinity.

According to a study by Rittler M., Liascovich R., Lopez-Camelo J. and Castilla E.E.[23], a significant association with parental consanguinity was observed for three congenital anomaly types: hydrocephalus, postaxial hand polydactyly, and bilateral cleft lip +/- cleft palate.

In the present study, congenital malformations like Valgus or varus deformity of foot, hypospadiasis and meningomyelocele were found to have higher incidence among non-consanguineous marriages. Thus, we infer that these disorders may be due to polygenic or multifactorial inheritance. This also shows that consanguinity can not be attributed to occurrence of many malformations except a few like cleft lip $\pm$ palate, anal atresia, preauricular tag, polydactyly

With regard to Prune belly syndrome, out of the three cases, in only 1 instance was the condition unequivocally due to consanguineous marriage. In the remaining cases, the disorders may be due to polygenic or multifactorial in origin. (3)

A case of Ehlers Danlos syndrome was noted in our study, which was also associated with consanguineous marriage. Another case was found to have achondroplasia, which had a positive association with parental consanguinity. Out of two cases of phocomelia, one was born to the consanguineous marriage and the other was to non- consanguineous marriage.

MATERNAL AGE & PARITY:

In our study the incidence of malformed babies was found to be significantly higher in the age group above 35 years, which is 8.13%. Regarding maternal age and malformations, study conducted by Patel Z.M. et. al. [(2)], the incidence of congenital malformations was higher in mothers > 35 years of age. This clearly shows that increased maternal age is a definite risk factor for congenital malformations.

But in the study by Vikram Datta et. al.[(1)], there was no correlation of congenital malformations with maternal age.

It was observed that there is increase in incidence of congenital malformations among mothers with parity four and above. In our study the incidence of malformed babies in mothers above parity 4 was 4.28%. Typically, maternal age can be a factor for parities of 4 and above (as pointed out earlier). The average maternal age of the group with parity of 4 and above was found to be less than 30. Therefore, the inference was that the risk of congenital malformation increases with the parity, regardless of maternal age.

CORRELATION OF ANTENATAL FACTORS WITH CONGENITAL MALFORMATIONS:

Any insult during the first trimester, the period of organogenesis, is likely to result in a malformed baby. The teratogenic effects of certain drugs like thalidomide were well known. In our study, 9.3% of mothers with the malformed babies gave history of drug intake. 7.6% of malformed cases had fever with or without rash.

The other factors which were evaluated in the previous study by Vikram Datta et. al.[1], and found to significantly increase the risk of congenital malformations were presence of hydramnios (7.3% of mothers with hydramnios gave birth to malformed babies) maternal febrile illness in the first trimester, past history of abortions (10 mothers) and history of progesterone intake during pregnancy (in 4 mothers out of which 1 had malformed baby).

In our study analysis of congenital malformations in mothers with febrile illness showed that there was an association of CNS malformations like encephalocele, hydrocephalus, meningomyelocele and midline facial defects like cleft lip +/- palate in mothers with history of fever. Western studies[9][10][11][12] have shown that on retrospective analysis, febrile illness during early weeks or months of pregnancy was associated with maldevelopment. Prospective analysis[11,12] failed to reveal any association.

Analysis of drug intake in the implication of congenital malformation revealed that intake of NSAID during antenatal period was associated with CNS and midline facial defects and inborn defects of ear . Among those patients who had taken drugs for termination, one had delivered a baby with hypospadiasis and two cases of prune belly syndrome.

According to Sipek A. et. al. [13], statistically significantly higher risk was found in 13 groups of diagnoses: anencephaly, inborn hydrocephalus, spina bifida, inborn defects of eyelids, lacrimal system and orbit, anophthalmos, microphthalmos and macrophthalmos, inborn defects of ear, congenital defects of the heart septum, congenital defects of great veins, cleft palate with cleft lip, congenital defect of gall bladder, biliary pathways and liver, congenital deformities of the hip, reduction deformities of upper extremity, congenital defects of muscular and skeletal system

Phil Young et. al.[14] noted an association between aspirin ingestion in the first trimester and cleft palate/lip in a retrospective, controlled study involving 599 children. The incidence of combined cleft lip and palate was 19.8% - nearly 4 times the rate in the control group. However, the significance of these findings is unclear as retrospective reporting is more likely to show a tendency towards malformations even when compared to a control group.

Phil Young et. al.[14] also noted that there was no evidence that NSAID was teratogenic when used in normal doses. The use of NSAID during pregnancy was not, however, without potential problems. The use of NSAID, even for short periods, after the 32nd week of pregnancy should be avoided due to a high incidence of premature closure of the ductus arteriosus. The use of NSAID particularly during the third trimester of pregnancy may cause a reduction in fetal urine output and consequent oligohydramnios resulting in fetal malformations.

It was obviously impossible to draw significant conclusions with clinical consequences on the basis of these results. The pregnant women should avoid, during the first trimester, all

drugs except those, which are carefully medically indicated and accepted as adequately safe.

On evaluation of maternal medical/ gynaecological illness, 327 people had no illness during antenatal period and 38 had illness. Out of 38 mothers, 21 had PIH, 7 had placenta previa, 4 had fibroid, 3 had GDM, 2 had heart disease and one had placental calcification. One case of Beckwith Weidman syndrome was reported. A case of arthrogryposis, which died in the neonatal period, was also reported. The common anomalies associated with PIH were CNS and genital anomalies.

Among 4 malformed babies born to mother with fibroid, one had valgus deformity and one had CTEV. This may be due to mechanical effects of fibroid on the foetus. This has a more risk of recurrence.

A case of Ehlers Danlos syndrome had been reported to a mother with placental calcification. Both the malformed babies born to heart disease patients had cleft lip +/- palate.

Out of three malformed babies born to a gestational diabetes mother, two had CTEV and one had caudal regression syndrome. This syndrome can also occur as a sporadic mutation. But this patient is a poorly controlled GDM patient. This should alert the patient and obstetrician for adequate care during next gestation.

The mothers of 21 malformed babies had oligohydramnios, Among these babies one had classical Potters hydramnios sequence, one had caudal regression syndrome and another had Prune belly syndrome. 16 mothers of malformed babies had polyhydramnios. They associated with anomalies like anencephaly, meningomyelocele or esophageal atresia.

BIRTH WEIGHT AND CONGENITAL MALFORMATIONS:

From the observed data, the incidence of congenital malformations was observed to be significantly more when the birth weight was less than 1.5kg.

According to Vikram Datta et. al.[1], thirteen of the 37 congenitally malformed babies (35.1%) were very low birth weight (mean ± SD: 1314.2 ± 175 g); 13/37 (35.1%) were low birth weights (mean ± SD: 1938.4 ± 268.8 g) and 11 (29.7%) were appropriate for gestational age (mean ± SD: 2866 ± 298.4 g).

SYSTEMIC DISTRIBUTION OF CONGENITAL MALFORMATIONS:

The commonest system involved in the present study was the musculoskeletal which was in conformity with the previous study by Vikram Datta et. al[1]. The next common systems in our study were GIT(7.59/1000 birth), CNS(3.88/1000 birth), genitourinary(3.55/1000 birth) However, some Indian workers had reported CNS defects as highest[5],[6] while one study has reported highest incidence of gastrointestinal malformations[7].

According to Bhat B.V. et. al.[8], musculo-skeletal malformations were the commonest (9.69 per 1000) followed by cutaneous (6.33 per 1000), genitourinary (5.47 per 1000), gastrointestinal (5.47 per 1000), central nervous system (3.99 per 1000) and cardiac anomalies (2.03 per 1000).

Analysis of individual anomalies showed that cleft lip +/-palate was the commonest one (4.29/1000 births) followed by polydactyly (3.79/1000 births), CTEV (2.69/1000 births), meningomyelocele (1.77/1000 births) and preauricular tag (1.52/1000 births).

PERINATAL MORTALITY AND CONGENITAL MALFORMATIONS:

Out of 365 cases of congenital anomalies, 39 died in the perinatal period. The major malformations responsible for perinatal mortality in our study were neural tube defects, exomphalos major, arthrogryposis and few syndromes like Edwards, Prune belly, caudal regression.

SYNDROMES:

Upon categorizing the malformations, ten syndromes were reported in our study. Three cases each of Edwards and Prune belly syndrome and one each of Ehlers Danlos, Beckwith Wiedemann, Caudal regression and Pierre Robins syndrome were noted.

SUMMARY AND CONCLUSION

- The incidence of malformations were significantly higher in babies born to mothers over the age of 35 years and with parity 4 and above.
- Majority of malformations had no significant antenatal risk factors like fever, drug intake, etc.
- There is no significant co-relation between consanguinity and congenital malformation.
- The incidence of malformations were significantly higher in stillbirths compared to live births.
- The incidence of malformations was significantly higher in male babies.
- The incidence of congenital malformations was observed to be more when the birth weight was less than 1.5kg.
- The commonest system involved was the musculoskeletal followed by gastrointestinal system.

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